Supplemental Information

Eligibility and Ineligibility Criteria

Ages Eligible for Study: 18 Years and older

Sexes Eligible for Study: Female

Inclusion Criteria:

Have a diagnosis of ovarian, fallopian tube, or primary peritoneal cancer patients who had a complete response to primary treatment with platinum based chemotherapy, have progressed within 6 months of completing platinum based chemotherapy and have subsequently received at least one, non-platinum-based, therapy

Have relapsed, refractory, or progressive disease following last line of treatment

Have estimated life expectancy of at least 3 months

Be willing and able to provide written informed consent/assent for the trial

Have measurable disease with at least 1 unidimensional lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) performance scale

Within 10 days of treatment initiation: Absolute neutrophil count (ANC) >= 1,500/mcL

Within 10 days of treatment initiation: Platelets >= 100,000/mcL

Within 10 days of treatment initiation: Hemoglobin >= 9 g/dL or >= 5.6 mmol/L without transfusion or erythropoietin (EPO) dependency (within 7 days of assessment)

Within 10 days of treatment initiation: Serum creatinine =< 1.5 X upper limit of normal (ULN) OR measured or calculated creatinine clearance (glomerular filtration rate [GFR] can also be used in place of creatinine or creatinine clearance [CrCl]) >= 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN

Within 10 days of treatment initiation: Serum total bilirubin =< 1.5 X ULN OR direct bilirubin =< ULN for subjects with total bilirubin levels > 1.5 ULN

Within 10 days of treatment initiation: Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase [SGPT]) =< 2.5 X ULN OR =< 5 X ULN for subjects with liver metastases

Within 10 days of treatment initiation: Albumin >= 2.5 mg/dL

Within 10 days of treatment initiation: International normalized ratio (INR) or prothrombin time (PT) =< 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or partial thromboplastin time (PTT) is within therapeutic range of intended use of anticoagulants

Within 10 days of treatment initiation: Activated partial thromboplastin time (aPTT) =< 1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication; if the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required

Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study

medication; subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year

Exclusion Criteria:

Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy within 4 weeks of the first dose of treatment

Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment

Short-term administration of systemic steroids (i.e., for allergic reactions or the management of immune related adverse events [irAEs]) is allowed

Has a known history of active TB (Bacillus tuberculosis)

Hypersensitivity to pembrolizumab or any of its excipients

Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study day 1 or who has not recovered (i.e., =< grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier

Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study day 1 or who has not recovered (i.e., =< grade 1 or at baseline) from adverse events due to a previously administered agent

Note: subjects with =< grade 2 neuropathy are an exception to this criterion and may qualify for the study

Note: if subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy

Has a known additional malignancy that is progressing or requires active treatment; exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer

Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis; subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment; this exception does not include carcinomatous meningitis which is excluded regardless of clinical stability

Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs); replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment

Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis

Has an active infection requiring systemic therapy

Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator

Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment

Clinically significant cardiovascular disease

Known severe hypersensitivity reactions to monoclonal antibodies or carboplatin >= grade 3, any history of anaphylaxis, or uncontrolled asthma

Has received prior therapy with pembrolizumab

Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies)

Has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (e.g., hepatitis C virus [HCV] ribonucleic acid [RNA] [qualitative] is detected)

Has received a live vaccine within 30 days of planned start of study therapy

Treatment plan, including administration schedule

Experimental: Treatment (pembrolizumab, carboplatin)
Patients receive pembrolizumab IV over 30 minutes on day 1 and carboplatin IV over 30 minutes on days 8 and 15. Courses repeat every 21 days for up to 24 months in the absence of disease progression or unacceptable toxicity.

Measurement of treatment effect including response criteria, definitions of response and survival, and methods of measurement

Progression-free survival (PFS) assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [Time Frame: 6 months]
Analyzed using the Kaplan-Meier method. Kaplan-Meier estimates of the survival function with 95% confidence intervals (CIs) at specific time points (using Greenwood's formula for the standard error) were computed. Comparisons with the historical control PFS will be conducted by examining whether the 95% confidence internal covers the historical control proportions.

1. Response rate (RR) assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [Time Frame: 6 months]

   The point estimate and the 95% exact CIs will be reported for RR. The comparison with the historical control rate will be conducted by examining whether the 95% confidence internal covers the historical control rate. Additional analyses will be conducted to evaluate in logistic regression models the odds ratio of response rate on predictors such as platinum-free interval, time to progression after previous platinum treatment, number of prior platinum regimens etc.

2. Incidence of adverse events evaluated by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [Time Frame: Up to 3.5 years]

   The safety population included all patients who received at least one dose of study medication. The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be utilized for adverse event reporting. The number and the percentage of patients who are removed from the study or altered dose regimen due to adverse effects will be reported.

3. PD-L1 expression of primary tumor blocks assessed by immunohistochemical staining [Time Frame: Up to 3.5 years]

4. Overall survival (OS) [Time Frame: Up to 3.5 years]

   Analyzed using the Kaplan-Meier method. Kaplan-Meier estimates of the survival function with 95% CIs at specific time points (using Greenwood's formula for the standard error) were computed. Comparisons with the historical control OS will be conducted by examining whether the 95% confidence internal covers the historical control proportions.

5. Best overall response (BOR) [Time Frame: Up to 3.5 years]
6. Progression-free survival (PFS) assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [Time Frame: Up to 3.5 years]

   Analyzed using the Kaplan-Meier method. Kaplan-Meier estimates of the survival function with 95% CIs at specific time points (using Greenwood's formula for the standard error) were computed. Comparisons with the historical control PFS will be conducted by examining whether the 95% confidence internal covers the historical control proportions.

7. Immune-related best overall response (BOR) assessed using irRECIST derived from Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [Time Frame: Up to 3.5 years]
8. Immune-related progression-free survival (PFS) irRECIST derived from Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [Time Frame: Up to 3.5 years]

Objectives

Primary Objectives

(1) **Objective:** To determine the clinical response rate of platinum chemotherapy and MK-3475 in platinum chemotherapy pretreated ovarian, fallopian tube, and primary peritoneal

(2) **Objective:** To examine whether retreatment with platinum chemotherapy in platinum resistant ovarian, fallopian tube, and primary peritoneal cancers improves progression free survival by concurrent administration of MK-3475.

Secondary Objectives

(1) **Objective**: To assess the safety and tolerability of concurrent administration of MK-3475 with platinum chemotherapy in patients with platinum resistant recurrent ovarian, fallopian tube, and primary peritoneal cancers.

(2) **Objective**: To determine the relationship between PD-L1 expression and response to the combination of MK-3475 and platinum

(3) **Objective**: To assess the overall survival of patients treated with the combination of MK- 3475 and platinum

Exploratory Objective

(1) **Objective:** To explore whether treatment with MK-3475 and platinum alters soluble factors in sera, peripheral immune responses and immune cell profile.

Dose Modification

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays).

Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Subjects will permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug have been previously held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Subjects will permanently discontinue drug for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table below.

Table. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	1. Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal
	Grade 4	Permanently discontinue		

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

				quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Carboplatin

Standard dose adjustments for carboplatin during treatment may be made based on changes in hepatic and renal function.

Some of the adverse events expected with carboplatin treatment are listed below.

1. Hematologic: Myelosuppression is the major dose-limiting toxicity

2. Hepatic toxicity: Elevated alkaline phosphatase, total bilirubin, and AST have been observed.

3. Allergic reactions: Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely anaphylaxis with bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

4. Neurologic: Peripheral neuropathy, ototoxicity, visual disturbances, change in taste, central nervous system symptoms

5. Gastrointestinal: Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea, weight loss, constipation, and gastrointestinal pain.

6. Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

STATISTICAL CONSIDERATION AND ANALYSIS PLAN

Sample size and power

Assume the response rate for the platinum re-treatment therapy in platinum pre-treated ovarian, fallopian tube, and primary peritoneal cancer patients is 23%. One of the primary objectives of this phase I/II trial is to test whether a new combinatory therapy (platinum + anti-PD1 antibody) can achieve a higher response rate (RR). We hypothesize that the true clinically significant response rate for the new therapy is 40~50%. The following table shows the sample size required to have either 80% or 90% power to declare statistical significance at level 0.05 for a true response rate at 40%, 45%, or 50%. A sample size of 27 patients will be required to have 80% power when the true response rate of the new combinatorial therapy is around 50%.

Response Rate of the new Therapy	**Power 80%**	**Power 90%**
40%	66	88
45%	41	54
50%	27	37

Furthermore, it is desirable to determine the response rate of the new combinatory therapy with sufficient precision. We can compute the standard error (SE) of the estimated response rates as the measure of precision for a range of true response rates. For the true response rate being in the range of 40%-50%, the SE does not vary much (0.07~0.09), and so there is adequate precision to detect the targeted response rate at 40-50%.

The median progression-free survival time is another efficacy endpoint of interest. Suppose the median progression-free survival time is 17, 20, or 23, and for the target sample size 27, the power to detect a statistically significant improvement in median progression-free survival time assuming accrual time is 1 year and the follow-up time is 1 year is listed in the following table. This table shows that our targeted sample size provides good power to detect 40% or more improvement in median progression-free survival time.

The median PFS in historical control	40% improvement in the new therapy	60% improvement in the new therapy
17 weeks	0.68	0.89
20 weeks	0.66	0.88
23 weeks	0.65	0.89

Statistical analysis plan

Clinical characteristics of the study cohort at the time of initial diagnosis will be tabulated, including age, stage, surgical optimality, and disease status after initial platinum therapy. The clinical characteristics and outcome of platinum-resistant patients will be also tabulated when retreated with the combinatory therapy.

The RR is the primary efficacy variable. The point estimate and the 95% exact confidence intervals will be reported for RR. The comparison with the historical control rate will be conducted by examining whether the 95% confidence internal covers the historical control rate. Additional analyses will be conducted to evaluate in logistic regression models the odds ratio of response rate on predictors such as platinum-free interval, time to progression after previous platinum treatment, number of prior platinum regimens etc. Other efficacy endpoints, which included progression free survival (PFS) and overall survival (OS), were also analyzed. Time-to-event variables were analyzed using the Kaplan-Meier method. Kaplan-Meier estimates of the survival function with 95% CIs at specific time points (using Greenwood's formula for the standard error) were computed. Comparisons with the historical control PFS and OS will be conducted by examining whether the 95% confidence internal covers the historical control proportions.

The safety population included all patients who received at least one dose of study medication. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

The number and the percentage of patients who are removed from the study or altered dose regimen due to adverse effects will be reported.